EFFECT OF TUFTSIN-LIKE HEPTAPEPTIDE WITH NOOTROPIC COMPONENT OF ACTION AND OF PIRACETAM ON AVOIDANCE CONDITIONING IN NORMAL RATS AND DURING CONFLICT SITUATION

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UDC 615.214.31:547.96].015.4:
612.821.1].3].076.9

Key Words: tuftsin-like heptapeptide; piracetam; avoidance reflex.

Both the nootropic drug piracetam and many peptide compounds, including those of the tuftsin group, have been shown to improve learning [7] or, conversely, to impair conditioned reflex formation of one or other type [1, 3]. The search for methods increasing the scope for studying the action of nootropic drugs is interesting in this connection, especially on account of the use of disturbances of function [4, 5]. In some investigations the learning process in an animal has been preceded by exposure to stress for this purpose [8] or the unambiguity of relations of cause and effect has been disturbed (electric shocks after formation of the avoidance reflex, i.e., worsening of the avoidance reflex) [2]. As was shown previously, tuftsin and some of its analogs improve the learning process, in a manner comparable with the action of psychostimulants of the nootropic group (meclofenoxate) [5], while at the same time lowering the level of negative emotional stress [4].

In the investigation described below the action of the most active synthetic peptide of the tuftsin group (the heptapeptide TP-1; synthesized at the Institute of Molecular Genetics; Head of Laboratory Candidate of Chemical Sciences V. N. Nezovibat'ko) and of piracetam on the formation and restoration of a conditioned avoidance reflex was compared when conditioning was abruptly disturbed by the creation of a stress-inducing conflict situation, arising on account of a change in cause and effect relations (lowering the reliability of the reflex).

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 180-200 g, kept in the animal house under natural conditions of light and darkness and with free access to water and food. The rats of group 1 ($n = 6$) were given the heptapeptide in a dose of 300 μg/kg 15 min before the experiment began, rats of group 2 ($n = 6$) were given physiological saline, rats of group 3 ($n = 5$) received piracetam in a dose of 500 mg/kg, and rats of group 4 ($n = 9$) received physiological saline. All substances were injected intraperitoneally in a volume of 1 ml. A conditioned avoidance reflex (CAR) was formed in all the animals in the course of 5 days by 20 daily sessions in a shuttle box. The conditioned stimulus was a sound of 800 Hz and the unconditioned stimulus an electric shock. The period between stimuli was 30-60 sec. On the 5th day the quality of the reflex was lowered by the method described previously [2], so that moving of the animal from one-half of the box to the other in response to the conditioned or unconditioned stimulus did not lead to disconnection of the current unlike in the experimental schedule adopted previously. The current was switched off immediately after the 3rd run, but the acoustic stimulus was discontinued only after 2 sec. Immediately after this disturbance of the experimental program, the previous schedule was reapplied (10 presentations).

Department of Higher Nervous Activity, Moscow University. Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR I. P. Ashmarin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 109, No. 5, pp. 445-446, May, 1990. Original article submitted May 3, 1989.

0007-4888/90/0005-0586$12.50

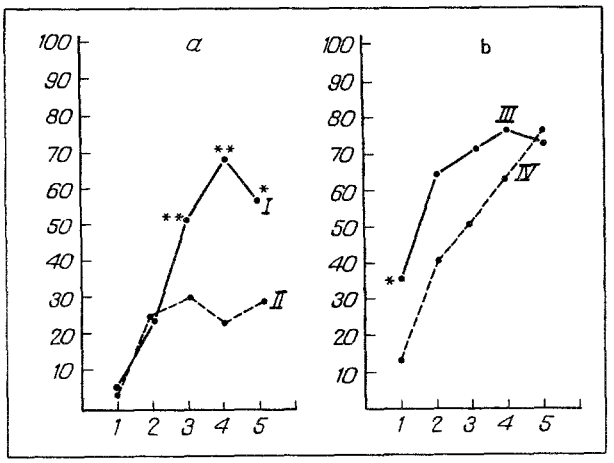

Fig. 1. Effect of heptapeptide and piracetam on CAR formation. Abscissa, days of experiments; ordinate, mean number of CAR (in %). I and II) Heptapeptide and physiological saline, respectively, III and IV) piracetam and physiological saline, respectively.

TABLE 1. Effect of Heptapeptide and Piracetam on Realization of CAR before and after Modification of Training Schedule ($M \pm m$)

Group of animals	Substance	Number of runs		Number of intertrial responses	
		before modification	after modification	before modification	after modification
1	Hepatapeptide	81,7±6,0	85,0±5,6	6,7±4,9	8,3±3,1
2	Physiological saline	61,7±11,1**	46,7±11,5	1,7±1,7*	3,3±2,1
3	Piracetam	82,0±9,2	68,0±15,3	14,0±5,1	18,0±8,0
4	Physiological saline	87,0±4,72	78,0±4,68	12,0±3,9	22,0±8,4

Legend. $*p < 0.05$, $**p < 0.01$ For data before and after modification of training program.

Considering the time course of CAR formation the total number of runs and of intertrial responses and the transformation of these parameters after modification of the training program, before and during the action of the heptapeptide and piracetam were analyzed. The numerical results were subjected to statistical analysis by Kolmogorov's nonparametric test on an "Amstrad" personal computer.

EXPERIMENTAL RESULTS

As will be clear from the data in Fig. 1, both the heptapeptide and piracetam significantly improved CAR formation, but exhibited some differences in the time course of its formation. For instance, a significant increase in the number of correct responses against the background of the heptapeptide (compared with the control) was achieved by the 2nd day, reaching a maximum by the 3rd day of training. When piracetam was used, a significant improvement was observed already on the 1st day, but later the degree of training was the same as in the control group.

Even a short period (according to the experimental schedule) with exposure of the rats to a conflict situation, caused by unambiguity of cause and effect relations, led to a sharp change of emotional state and disturbed the CAR formed previously. Against a background of restless movements and vocal responses, the number of intertrial runs from one-half of the box to the other increased and the number of CAR fell sharply ($p < 0.01$; Table 1), evidence of increased emotional stress of the animals [2, 6]. Against this background, maintenance of the standard schedule of avoidance conditioning did not restore the initial level of training of the animals. These results confirm the conclusion that the disturbances of reproduction of the reflex were due to ambiguity of cause and effect relations [9].

Preliminary injection of the heptapeptide largely prevented the development of the disturbance of CAR formation in this particular conflict situation. It will be clear from Table 1 that the number of intertrial responses increased but not significantly, whereas the number of CAR not only was not reduced but actually increased somewhat. Piracetam had a similar action. However, its protective action was much weaker.

Thus the synthetic heptapeptide of the tuftsin group facilitates CAR formation and prevents responses under conditions of a conflict situation of acute stress, and it is more effective in this respect than the classical nootropic agent piracetam, which has a similar action.

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